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Transmitted herewith for filing is a **CONTINUATION-IN-PART** application of **U.S.S.N. 08/692,113**

of: JEANNIN, Philippe
for: INSECTICIDAL COMBINATION TO CONTROL MAMMAL FLEAS, IN PARTICULAR FLEAS ON CATS AND DOGS

Enclosed are the following:

[XXX] Specification, abstract and claims of 29 pages

[XXX] No drawings.

[XXX] Declaration signed by the named inventor(s)

[ ] Letter: Identifying Inventor(s) for New Application

[ ] Small Entity Statement

[XXX] Assignment Papers

[XXX] Certified Copy of Priority Document(s)

[XXX] Preliminary Amendment (reducing the filing fee)

The filing fee is calculated below (after reduction for preliminary amendment if noted above).

[X] Total claims:	48	-	20	=	28	x	$ 22.00	= $ 616.00
[X] Independent claims:	02	-	3	=	*	x	$ 80.00	= $
[ ] Multiple dependent claim(s)						+	$260.00	= $
							BASIC FEE	= $ 770.00
							TOTAL OF ABOVE CALCULATIONS	= $1386.00
[ ] Reduction by 1/2 for filing by small entity								− $[ ]
							SUBTOTAL	= $1386.00
[ ] Fee for recording of assignment								+ $ 40.00
TOTAL OF FILING AND ASSIGNMENT RECORDING FEES								= **$1426.00**

[XXX] A check in the amount of $1426.00 is enclosed. If no check or an insufficient check is enclosed and a fee is due herewith, the Commissioner is authorized to charge any fee or additional fee due in connection herewith to Deposit Account No. 12-0555. A duplicate of this sheet is enclosed.

Respectfully submitted,

Date: May 27, 1997

Douglas E. Jackson

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The present invention relates to an improvement to the processes for controlling mammal fleas and in particular fleas on cats and dogs. The invention also relates to a novel composition for this use, based on a synergistic combination of parasiticides which are already known. Lastly, the invention relates to the use of such already-known parasiticides for the preparation of such a composition.

A novel class of 1-N-arylpyrazole-based insecticides has been described in patents EP-A-295,217 and EP-A-352,944. The compounds of the classes defined in these patents are highly active, and one of these compounds

1-[2,6-Cl_2 4-CF_3 phenyl]3-CN 4-[SO-CF_3]5-NH_2 pyrazole,

whose common name is fipronil, has proven to be particularly effective not only against crop parasites but also against mammal ectoparasites and in particular, but not exclusively, fleas, ticks, flies and myiases.

Compounds with an ovicidal and/or larvicidal effect on the immature stages of various ectoparasites are already known, for example from patent US-A-5,439,924. Among these compounds are featured insect growth regulator compounds (IGR) which act either by blocking the development of the immature stages (eggs and larvae) into adult stages, or by inhibiting the synthesis of chitin.

Patent FR-A-2,713,889 is moreover known, which generally describes the combination of at least one compound of IGR (insect growth regulator) type, comprising compounds with juvenile hormone activity and chitin synthesis inhibitors, with at least one of three N-aryldiazole compounds, in particular fipronil, to control many harmful insects belonging to very varied orders.

The compositions may be used in very diverse forms, although the applications, for example veterinary, healthcare or plant-protection applications, for which these different forms are

designed are not specified, nor are the parasites for which they are respectively intended.

The only application which may be thought to be veterinary is associated with the example of the manufacture of a pesticidal collar which is a slow-release formulation.

The invention proposes to improve the processes for controlling fleas in small mammals, and in particular in cats and dogs.

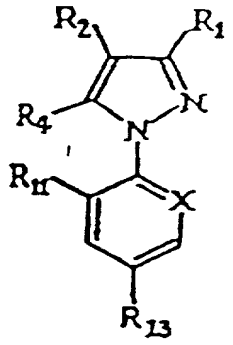
The object of the invention is, in particular, to use already-known parasiticides in order to prepare a composition which is highly active against the fleas of these animals.

Lastly, the object of the invention is a novel composition thus prepared and intended, in particular, to control fleas.

For the purposes of the present invention, the term flea is understood to refer to all the usual or accidental species of parasitic flea of the order Siphonaptera, and in particular the species Ctenocephalides, in particular C. felis and C. canis, rat fleas (Xenopsylla cheopis) and human fleas (Pulex irritans).

The very high efficacy of the process and of the composition according to the invention implies not only high immediate efficacy but also very long-lasting efficacy after the animal has been treated.

The subject of the invention is a process for controlling the fleas of small mammals, and in particular cats and dogs, over a long period, characterized in that the animal is treated by locally depositing on the skin, preferably localized over a small surface area (spot-on application), in parasiticidally effective doses and proportions, on the one hand at least one compound (A) belonging to formula (I),



(I)

in which:

R_1 is CN or methyl or a halogen atom;

R_2 is $S(O)_nR_3$ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

R_3 is alkyl or haloalkyl;

R_4 represents a hydrogen or halogen atom; or a member of a group consisting of NR_5R_6, $S(O)_mR_7$, $C(O)R_7$, $C(O)O-R_7$, alkyl, haloalkyl, OR_8 and $-N=C(R_9)$ (R_{10});

R_5 and R_6 independently represent a hydrogen atom or an alkyl, haloalkyl, C(O)alkyl, alkoxycarbonyl or $S(O)_r-CF_3$ radical; or R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms such as oxygen or sulphur;

R_7 represents an alkyl or haloalkyl radical;

R_8 represents an alkyl or haloalkyl radical or a hydrogen atom;

R_9 represents an alkyl radical or a hydrogen atom;

R_{10} represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or a member of the group consisting of OH, -O-alkyl, S-alkyl, cyano and alkyl;

R_{11} and R_{12} represent, independently of each other, a hydrogen or halogen atom, or possibly CN or NO_2;

R_{13} represents a halogen atom or a haloalkyl, haloalkoxy, $S(O)_qCF_3$ or SF_5 group;

m, n, q and r represent, independently of each other, an integer equal to 0, 1 or 2

X represents a trivalent nitrogen atom or a radical C-R_{12}, the other three valency positions of the carbon atom forming part of the aromatic ring

with the proviso that when R_1 is methyl, either R_3 is haloalkyl, R_4 is NH_2, R_{11} is Cl, R_{13} is CF_3 and X is N; or R_2 is 4,5-dicyanoimidazol-2-yl, R_4 is Cl, R_{11} is Cl, R_{13} is CF_3 and X is =C-Cl;

and, on the other hand at least one compound (B), of IGR (insect growth regulator) type, in a fluid vehicle which is acceptable for the animal and suitable for local application on the skin.

Preferably, one uses at least one compound (A) belonging to the formula (I) in which:

R_1 is CN or methyl

R_2 is $S(O)_nR_3$

R_3 is alkyl or haloalkyl

R_4 represents a hydrogen or halogen atom; or a radical NR_5R_6, $S(O)_mR_7$, $C(O)R_7$, alkyl, haloalkyl or OR_8 or a radical $-N=C(R_9)(R_{10})$

R_5 and R_6 independently represent a hydrogen atom or an alkyl, haloalkyl, C(O)alkyl or $S(O)_r$-CF_3 radical; or R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms such as oxygen or sulphur

R_7 represents an alkyl or haloalkyl radical

R_8 represents an alkyl or haloalkyl radical or a hydrogen atom

R_9 represents an alkyl radical or a hydrogen atom

R_{10} represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or groups such as OH, -O-alkyl, S-alkyl, cyano or alkyl

R_{11} and R_{12} represent, independently of each other, a hydrogen or halogen atom

R_{13} represents a halogen atom or a haloalkyl, haloalkoxy, $S(O)_qCF_3$ or SF_5 group

m, n, q and r represent, independently of each other, an integer equal to 0, 1 or 2

X represents a trivalent nitrogen atom or a radical C-R_{12}, the other three valency positions of the carbon atom forming part of the aromatic ring

with the proviso that when R_1 is methyl, then R_3 is haloalkyl, R_4 is NH_2, R_{11} is Cl, R_{13} is CF_3 and X is N.

Compounds of formula (I) in which R_1 is CN will be selected most particularly. Compounds in which R_2 is $S(O)_nR_3$, preferably with n = 1, R_3 preferably being CF_3 or alkyl, for example methyl or ethyl, or alternatively n = 0, R_3 preferably being CF_3, as well as those in which X = C-R_{12}, R_{12} being a halogen atom, will also be selected. Compounds in which R_{11} is a halogen atom and those in which R_{13} is haloalkyl, preferably CF_3, are also preferred. Within the context of the present invention, compounds which combine two or more of these characteristics will advantageously be selected.

A preferred class of compounds of formula (I) consists of compounds such that R_1 is CN, R_3 is haloalkyl, R_4 is NH_2, R_{11} and R_{12} are, independently of each other, a halogen atom, and/or R_{13} is haloalkyl. Preferably also, X is C-R_{12}.

In these compounds, R_3 preferably represents CF_3 or ethyl.

In the present invention, the alkyl radicals may contain generally from 1 to 6 carbon atoms. The ring formed by the divalent alkylene radical representing R_5 and R_6, as well as the nitrogen atom to which R_5 and R_6 are attached, may be generally a 5-, 6- or 7-membered ring.

A compound of formula (I) which is most particularly preferred in the invention is 1-[2,6-Cl_2 4-CF_3phenyl]3-CN 4-[SO-CF_3] 5-NH_2 pyrazole, the common name of which is fipronil.

The two compounds which differ from the above by the following characteristics:

1- n = 0, R_3 = CF_3

2- n = 1, R_3 = ethyl.

may also be mentioned.

Among the compounds (B), mention may be made in particular of compounds which mimic juvenile hormones, in particular:

azadirachtin - Agridyne
diofenolan (Ciba Geigy)
fenoxycarb (Ciba Geigy)
hydroprene (Sandoz)
kinoprene (Sandoz)
methoprene (Sandoz)
pyriproxyfen (Sumitomo/Mgk)
tetrahydroazadirachtin (Agridyne)
4-chloro-2-(2-chloro-2-methylpropyl)-5-(6-iodo-3-pyridylmethoxy)pyridizin-3(2H)-one

and chitin-synthesis inhibitors, in particular:

chlorfluazuron (Ishihara Sangyo)
cyromazine (Ciba Geigy)
diflubenzuron (Solvay Duphar)
fluazuron (Ciba Geigy)
flucycloxuron (Solvay Duphar)
flufenoxuron (Cyanamid)
hexaflumuron (Dow Elanco)
lufenuron (Ciba Geigy)
tebufenozide (Rohm & Haas)
teflubenzuron (Cyanamid)
triflumuron (Bayer)

these compounds being defined by their international common name (The Pesticide Manual, 10th edition, 1994, Ed. Clive Tomlin, Great Britain).

As chitin-synthesis inhibitors, mention may also be made of compounds such as 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenylurea, 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(1,1,2,2-tetrafluoroethoxy)phenylurea and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-trifluoromethyl)phenylurea.

Novaluron (Isagro, Italian company) may also be mentioned as a compound (B).

The preferred compounds (B) are methoprenes, pyriproxyfens, hydroprene, cyromazine, lufenuron and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenylurea.

Another preferred compound (B) is again novaluron.

It is preferable for the administration of the two types of compound to be concomitant and preferably simultaneous.

It is preferable for the treatment according to the invention to be carried out every two or, preferably, every three months on cats and dogs.

Preferably, the treatment is carried out so as to administer to the animal a dose of from 0.1 to 40 and in particular from 1 to 20 mg/kg of derivative (A) and a dose of from 0.1 to 40 and in particular 1 to 30 mg/kg of compound (B).

The preferred doses are from 5 to 15 mg/kg for compound (A) and from 0.5 to 15 mg/kg for the preferred compounds (B), or 10 to 20 mg/kg for the other compounds (B).

In another embodiment of the process according to the invention, compounds (A) and (B) may be applied in a distinct and separate manner over time. In this case, it is preferred to alternate the applications with an interval, for example of one month between two applications, the first application preferably being made with compound (A).

It is understood that the dosage values which are thus indicated are average values which may vary within a wide range, since, in practice, a formulation having defined doses of compound (A) of 1-N-phenylpyrazole-type derivative and of compound (B) will be administered to animals having relatively different weights. Consequently, the doses actually applied are often smaller or larger by a factor which may be up to 2, 3 or 4 relative to the preferred dose, without entailing any toxic risk for the animal in the case of an overdose, and while at the same time

retaining real efficacy, possibly of shorter duration, in the case of an underdose.

The object of this process is non-therapeutic and relates in particular to the cleaning of animal hairs and skin by elimination of the parasites which are present, as well as their residues and dejections. The treated animals thus have hair which is more pleasant to look at and to feel. This also allows one to avoid the development of fleas in the house.

The invention also relates to such a process for therapeutic purposes, which is intended to treat and prevent parasitoses having pathogenic consequences.

In accordance with the present invention, the process described above may also be used to control ectoparasites, in particular ticks.

The subject of the invention is also a composition, in particular one for controlling fleas on small mammals, characterized in that it includes, on the one hand, at least one compound (A) of formula (I) as defined above, and, on the other hand, at least one compound (B) defined above, in doses and proportions which have parasiticidal efficacy on fleas, in a fluid vehicle which is acceptable for the animal and convenient for local application to the skin, preferably localized over a small surface area.

Preferably, in formula (I);

R_1 is CN or methyl

R_2 is $S(O)_nR_3$

R_3 is alkyl or haloalkyl

R_4 represents a hydrogen or halogen atom; or a radical NR_5R_6, $S(O)_mR_7$, $C(O)R_7$, alkyl, haloalkyl or OR_8 or a radical $-N=C(R_9)\ (R_{10})$

R_5 and R_6 independently represent a hydrogen atom or an alkyl, haloalkyl, C(O)alkyl or $S(O)_r-CF_3$ radical; or R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms such as oxygen or sulphur

R_7 represents an alkyl or haloalkyl radical

R_8 represents an alkyl or haloalkyl radical or a hydrogen atom

R_9 represents an alkyl radical or a hydrogen atom

R_{10} represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or groups such as OH, -O-alkyl, S-alkyl, cyano or alkyl

R_{11} and R_{12} represent, independently of each other, a hydrogen or halogen atom

R_{13} represents a halogen atom or a haloalkyl, haloalkoxy, $S(O)_qCF_3$ or SF_5 group

m, n, q and r represent, independently of each other, an integer equal to 0, 1 or 2

X represents a trivalent nitrogen atom or a radical C-R_{12}, the other three valency positions of the carbon atom forming part of the aromatic ring

with the proviso that when R_1 is methyl, then R_3 is haloalkyl, R_4 is NH_2, R_{11} is Cl, R_{13} is CF_3 and X is N.

Compounds of formula (I) in which R_1 is CN will be selected most particularly. Compounds in which R_2 is $S(O)_nR_3$, preferably with n = 1, R_3 preferably being CF_3 or alkyl, for example methyl or ethyl, or alternatively n = 0, R_3 preferably being CF_3, as well as those in which X = C-R_{12}, R_{12} being a halogen atom, will also be selected. Compounds in which R_{11} is a halogen atom and those in which R_{13} is haloalkyl, preferably CF_3, are also preferred. Within the context of the present invention, compounds which combine two or more of these characteristics will advantageously be selected.

A preferred class of compounds of formula (I) consists of compounds such that R_1 is CN, R_3 is haloalkyl, R_4 is NH_2, R_{11} and R_{12} are, independently of each other, a halogen atom, and/or R_{13} is haloalkyl.

In these compounds, R_3 preferably represents CF_3 or ethyl.

A compound of formula (I) which is most particularly preferred in the invention is 1-[2,6-Cl_2 4-CF_3phenyl]3-CN 4-[SO-CF_3] 5-NH_2 pyrazole.

The two compounds which differ from the above by the following characteristics:

1- n = 0, $R_3 = CF_3$

2- n = 1, R_3 = ethyl

may also be mentioned.

The compounds of formula (I) may be prepared according to one or other of the processes described in patent applications WO-A-87/3781, 93/6089, 94/21606 or European patent application EP-A-0,295,117, or any other process which falls within the competence of a specialist skilled in the art of chemical synthesis. For the chemical preparation of the products of the invention, a person skilled in the art is considered as having at his disposal, inter alia, all of the contents of "Chemical Abstracts" and the documents cited therein.

Among the compounds of IGR type listed above, methoprenes, pyriproxyfens, hydroprene, cyromazine, lufenuron and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenylurea are preferred.

Novaluron is also preferred.

The proportions, by weight, of compounds of formula (I) and of compound (B) are preferably between 80/20 and 20/80.

The fluid vehicle may be simple or complex and it is adapted to the route and mode of administration selected.

The compositions for spot-on application can advantageously comprise:

b) a crystallization inhibitor, in particular one which is present in a proportion of from 1 to 20% (W/V), preferably from 5 to 15%, this inhibitor satisfying the test according to which:

0.3 ml of a solution A comprising 10% (W/V) of the compound of formula (I) in the solvent defined in c) below, along with 10% of this inhibitor, are deposited on a glass slide at 20°C for 24 hours, after which it is observed with the naked eye that there are few or no

crystals, in particular fewer than 10 crystals, preferably 0 crystals on the glass slide,

c) an organic solvent having a dielectric constant of between 10 and 35, preferably of between 20 and 30, the content of this solvent c) in the overall composition preferably representing the difference to make the composition up to 100%,

d) an organic cosolvent having a boiling point of below 100°C, preferably of below 80°C, and having a dielectric constant of between 10 and 40, preferably of between 20 and 30; this cosolvent may advantageously be present in the composition in a d)/c) weight/weight (W/W) ratio of between 1/15 and 1/2. The solvent is volatile, so as to serve in particular as a drying promoter, and is miscible with water and/or with the solvent c).

Although this is not preferred, the composition for spot-on application may optionally comprise water, in particular in a proportion of from 0 to 30% (volume per unit volume, V/V), in particular from 0 to 5%.

The composition for spot-on application may also comprise an antioxidant intended to inhibit air-oxidation, this agent being present in particular in a proportion of from 0.005 to 1% (W/V), preferably from 0.01 to 0.05%.

The compositions according to the invention intended for pets, in particular cats and dogs, are generally applied by being deposited onto the skin ("spot-on" or "pour-on" application); this is generally a localized application over a surface area of less than 10 cm^2, especially of between 5 and 10 cm^2, in particular at two points and preferably localized between the animal's shoulders. Once deposited, the composition diffuses, in particular over the animal's entire body, and then dries without crystallizing or modifying the appearance (in particular absence of any whitish deposit or dusty appearance) or the feel of the fur.

The compositions for spot-on application according to the invention are particularly advantageous owing to their efficacy, their speed of action and the pleasant appearance of the animal's fur after application and drying.

As organic solvent c) which can be used in the invention, mention may be made in particular of: acetone, acetonitrile, benzyl alcohol, butyl diglycol, dimethylacetamide, dimethylformamide, dipropylene glycol n-butyl ether, ethanol, isopropanol, methanol, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, monomethylacetamide, dipropylene glycol monomethyl ether, liquid polyoxyethylene glycols, propylene glycol, 2-pyrrolidone, in particular N-methylpyrrolidone, diethylene glycol monoethyl ether, ethylene glycol and diethyl phthalate, or a mixture of at least two of these solvents.

As crystallization inhibitor b) which can be used in the invention, mention may be made in particular of:

- polyvinylpyrrolidone, polyvinyl alcohols, copolymers of vinyl acetate and vinylpyrrolidone, polyethylene glycols, benzyl alcohol, mannitol, glycerol, sorbitol, polyoxyethylenated sorbitan esters; lecithin, sodium carboxymethylcellulose, acrylic derivatives such as methacrylates and the like,

- anionic surfactants such as alkaline stearates, in particular sodium, potassium or ammonium stearate; calcium stearate; triethanolamine stearate; sodium abietate; alkyl sulphates, in particular sodium lauryl sulphate and sodium cetyl sulphate; sodium dodecylbenzenesulphonate, sodium dioctylsulphosuccinate; fatty acids, in particular those derived from coconut oil,

- cationic surfactants such as water-soluble quaternary ammonium salts of formula $N^+R'R''R'''R'''',Y^-$ in which the radicals R are optionally hydroxylated hydrocarbon radicals and Y^- is an anion of a strong acid such as the halide, sulphate and sulphonate anions;

cetyltrimethylammonium bromide is among the cationic surfactants which can be used,

- amine salts of formula $N^+R'R''R'''$ in which the radicals R are optionally hydroxylated hydrocarbon radicals; octadecylamine hydrochloride is among the cationic surfactants which can be used,

- nonionic surfactants such as optionally polyoxyethylenated sorbitan esters, in particular polysorbate 80, polyoxyethylenated alkyl ethers; polyethylene glycol stearate, polyoxyethylenated derivatives of castor oil, polyglycerol esters, polyoxyethylenated fatty alcohols, polyoxyethylenated fatty acids, copolymers of ethylene oxide and propylene oxide,

- amphoteric surfactants such as substituted lauryl compounds of betaine,

or preferably a mixture of at least two of these crystallization inhibitors.

In a particularly preferred manner, a crystallization inhibitor couple, namely the combination of a film-forming agent of polymeric type and a surfactant, will be used. These agents will be chosen in particular from the compounds mentioned as crystallization inhibitor b).

Among the film-forming agents of polymeric type which are particularly advantageous, mention may be made of:

- the various grades of polyvinylpyrrolidone,
- polyvinyl alcohols, and
- copolymers of vinyl acetate and vinylpyrrolidone.

As regards the surfactants, mention will be made most particularly of nonionic surfactants, preferably polyoxyethylenated sorbitan esters and in particular the various grades of polysorbate, for example polysorbate 80.

The film-forming agent and the surfactant may be incorporated, in particular, in similar or identical

amounts within the limit of the total amounts of crystallization inhibitor mentioned elsewhere.

The couple thus produced ensures the objectives of absence of crystallization on the hairs and maintenance of the cosmetic appearance of the coat in a noteworthy manner, that is to say without any tendency towards stickiness or to a sticky appearance, despite the high concentration of active material.

As cosolvent d), mention may be made in particular of: absolute ethanol, isopropanol, methanol.

As antioxidant, standard agents are used in particular, such as: butylhydroxyanisole, butylhydroxytoluene, ascorbic acid, sodium metabisulphite, propyl gallate and sodium thiosulphate, or a mixture of not more than two of these agents.

The compositions for spot-on application according to the invention are usually prepared by simple mixing of the constituents as defined earlier; advantageously, to begin with, the active material is mixed in the main solvent and the other ingredients or adjuvants are then added.

The volume applied may be from about 0.3 to 1 ml, preferably about 0.5 ml for cats, and from about 0.3 to 3 ml for dogs, according to the weight of the animal.

In a particularly preferred manner, the composition according to the invention may be in the form of a concentrated emulsion, suspension or solution for spot-on application to a small area of the animal's skin, generally between the two shoulders (spot-on type solution). In a clearly less preferred manner, forms of solution or suspension to be sprayed, forms of solution, suspension or emulsion to be poured or spread onto the animal (pour-on type solution) an oil, a cream, an ointment or any other fluid formulation for topical administration may be provided.

Advantageously, the ready-to-use composition contains a dose of from 0.1 to 40 mg/kg of compound (A) of formula (I) and 0.1 to 40 mg/kg of compound (B).

Preferably, a ready-to-use dosed formulation, in particular one for spot-on application, contains 1 to 20 mg/kg, preferably 2 to 10 mg/kg of compound (A), in particular fipronil, and from 1 to 30 mg/kg, preferably 2 to 10 mg/kg, of preferred compound (B) or 10 to 20 mg/kg of other compound (B).

Advantageously, ready-to-use compositions dosed for 1-10, 10-20 and 20-40 kg animals respectively may be provided.

In another embodiment, provided for separate application over time, a composition may be made in the form of a kit separately combining, in the same packaging, a composition containing a compound of formula (I), in particular fipronil, and a composition containing compound (B), preferably pyriproxyfen, each of the compositions including a vehicle which allows it to be applied onto the skin.

Preferably, each of the two compositions is provided for local spot-on application and, preferably, a container containing just the dose required is provided for each application.

Thus, for example, a kit may contain, in a package, three containers each containing a single dose of composition of compound (A) and three containers each containing a single dose of composition of compound (B), the containers (A) being distinguished from the containers (B) by markings, shapes or colours, as well as a notice specifying that the containers (A) and (B) must be used alternately with an interval, for example, of one month, and starting, for example, with a container (A).

The compositions according to the invention, in particular those for spot-on application, have proven to be extremely effective for the very long-lasting treatment of fleas on mammals, and in particular small mammals such as cats and dogs.

The discovery that the compound (A), such as fipronil, dissolves in the sebum so as to cover the entire animal and becomes concentrated in the sebaceous

glands, from which it is gradually released over a very long period, is a plausible explanation of this long-lasting efficacy for these compositions, and could perhaps also explain the long-lasting action of the associated compound (B).

They also have a certain efficacy against other parasitic insects and, in particular, ticks, and it is understood that the application of the composition according to the invention may be extended to the treatment of ectoparasites, or even endoparasites for which the composition proves to have real utility capable of being obtained practically, according to the criteria of the veterinary art.

Thus, for example, a composition based on fipronil and fluazuron may also be used in particular against ticks.

Where appropriate, the composition according to the invention may also comprise another insecticide, and in particular imidaclopride.

The subject of the invention is also the use of at least one compound (A) of formula (I) and of at least one compound (B) of IGR type, as defined above, for the preparation of a composition as defined above.

Other advantages and characteristics of the invention will become apparent on reading the description which follows, which is given by way of non-limiting example.

The composition preparation example which follows includes, as compound (A) of formula (I), the compound known as fipronil.

By way of example to prepare a composition for local application to the skin according to the invention, the following components may advantageously be mixed together:

a1 - compound (B) in a proportion of from 1 to 20% (percentage as a weight per unit volume W/V)

a2 - compound (A) of formula (I), in a proportion of from 1 to 20%, preferably 5 to 15% (percentage as a weight per unit volume W/V).

By way of example, the compositions according to the invention comprise the following concentrations (W/V) of compounds (A) and (B) in a liquid medium comprising a representative of each of the components b, c and d. The total volume is 1 ml.

Example 1
fipronil 10%
pyriproxyfen 5%

Example 2
fipronil 5%
pyriproxyfen 5%

Example 3
fipronil 5%
pyriproxyfen 20%

Example 4
fipronil 10%
methoprene 30%

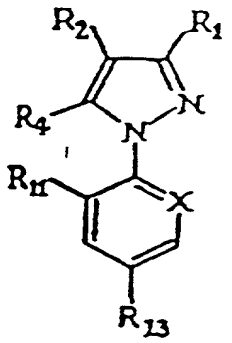
Example 5
fipronil 10%
1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-trifluoromethyl)phenylurea 5%.

Cats are infested with 100 fleas each, and are then reinfested every 10 days. Concomitant with the first manifestation, they receive a local skin application of 0.1 ml/kg of the composition according to Example 1. Two months after the treatment and ten days after the last infestation, no fleas are detected and the eggs collected are found to be non-viable.

Dogs treated according to the same procedure with compositions according to Examples 1 and 2 show the same efficacy of treatment two months after application of the composition.

CLAIMS

1. Composition for long-lasting protection against fleas on small mammals, and in particular cats and dogs, characterized in that it includes, on the one hand, at least one compound (A) belonging to the formula (I),



(I)

in which:

R_1 is CN or methyl or a halogen atom;

R_2 is $S(O)_nR_3$ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

R_3 is alkyl or haloalkyl;

R_4 represents a hydrogen or halogen atom; or a radical NR_5R_6, $S(O)_mR_7$, $C(O)R_7$, $C(O)O-R_7$, alkyl, haloalkyl or OR_8 or a radical $-N=C(R_9)(R_{10})$;

R_5 and R_6 independently represent a hydrogen atom or an alkyl, haloalkyl, C(O)alkyl, alkoxycarbonyl or $S(O)_r-CF_3$ radical; R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms such as oxygen or sulphur;

R_7 represents an alkyl or haloalkyl radical;

R_8 represents an alkyl or haloalkyl radical or a hydrogen atom;

R_9 represents an alkyl radical or a hydrogen atom;

R_{10} represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or groups such as OH, -O-alkyl, S-alkyl, cyano or alkyl;

R_{11} and R_{12} represent, independently of each other, a hydrogen or halogen atom, or optionally CN or NO_2

R_{13} represents a halogen atom or a haloalkyl, haloalkoxy, $S(O)_qCF_3$ or SF_5 group;

m, n, q and r represent, independently of each other, an integer equal to 0, 1 or 2;

X represents a trivalent nitrogen atom or a radical $C-R_{12}$, the other three valency positions of the carbon atom forming part of the aromatic ring;

with the proviso that when R_1 is methyl, then R_3 is haloalkyl, R_4 is NH_2, R_{11} is Cl, R_{13} is CF_3 and X is N; or R_2 is 4,5-dicyanoimidazol-2-yl, R_4 is Cl, R_{11} is Cl, R_{13} is CF_3 and X is =C-Cl;

and, on the other hand, at least one ovicidal compound (B), of insect growth regulator (IGR) type, in a fluid vehicle which is acceptable to the animal and suitable for local application on the skin.

2. Composition according to claim 1, characterized in that the compound of formula (I) is such that:

R_1 is CN or methyl

R_2 is $S(O)_nR_3$

R_3 is alkyl or haloalkyl

R_4 represents a hydrogen or halogen atom; or a radical NR_5R_6, $S(O)_mR_7$, $C(O)R_7$, alkyl, haloalkyl or OR_8 or a radical $-N=C(R_9)\ (R_{10})$

R_5 and R_6 independently represent a hydrogen atom or an alkyl, haloalkyl, C(O)alkyl or $S(O)_r-CF_3$ radical; or R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms such as oxygen or sulphur

R_7 represents an alkyl or haloalkyl radical

R_8 represents an alkyl or haloalkyl radical or a hydrogen atom

R_9 represents an alkyl radical or a hydrogen atom

R_{10} represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or groups such as OH, -O-alkyl, S-alkyl, cyano or alkyl

R_{11} and R_{12} represent, independently of each other, a hydrogen or halogen atom

R_{13} represents a halogen atom or a haloalkyl, haloalkoxy, $S(O)_qCF_3$ or SF_5 group

m, n, q and r represent, independently of each other, an integer equal to 0, 1 or 2

X represents a trivalent nitrogen atom or a radical $C-R_{12}$, the other three valency positions of the carbon atom forming part of the aromatic ring

with the proviso that when R_1 is methyl, then R_3 is haloalkyl, R_4 is NH_2, R_{11} is Cl, R_{13} is CF_3 and X is N.

3. Composition according to claim 1, characterized in that the compound of formula (I) is such that R_1 is CN.

4. Composition according to claim 1, characterized in that the compound of formula (I) is such that R_{13} is haloalkyl, preferably CF_3.

5. Composition according to claim 1, characterized in that the compound of formula (I) is such that R_2 is $S(O)_nR_3$, preferably with n = 1, R_3 preferably being CF_3 or alkyl, in particular methyl or ethyl, or n = 0, R_3 preferably being CF_3.

6. Composition according to claim 1, characterized in that the compound of formula (I) is such that X is $C-R_{12}$ with R_{12} being a halogen atom.

7. Composition according to claim 1, in which the compound of formula (I) is such that R_1 is CN, R_3 is haloalkyl, R_4 is NH_2, R_{11} and R_{12} are, independently of each other, a halogen atom, and/or R_{13} is haloalkyl.

8. Composition according to claim 1, in which the compound of formula (I) is:

1-[2,6-Cl_2 4-CF_3 phenyl] 3-CN 4-[SO-CF_3]5-NH_2 pyrazole.

9. Composition according to claim 1, in which the compound of formula (I) is one of the following compounds:

1: 1-[2,6-Cl_2 4-CF_3 phenyl] 3-CN 4-[S-CF_3]5-NH_2 pyrazole

2: 1-[2,6-Cl_2 4-CF_3 phenyl] 3-CN 4-[SO-C_2H_5]5-NH_2 pyrazole

10. Composition according to claim 1, characterized in that the compound (B) is a compound which mimics juvenile hormones, in particular:

azadirachtin
diofenolan
fenoxycarb
hydroprene
kinoprene
methoprene
pyriproxyfen
tetrahydroazadirachtin
and 4-chloro-2-(2-chloro-2-methyl-propyl)-5-(6-iodo-3-pyridylmethoxy)pyridizine-3(2H)-one

or a chitin-synthesis inhibitor, in particular:

chlorfluazuron
cyromazine
diflubenzuron
fluazuron
flucycloxuron
flufenoxuron
hexaflumuron
lufenuron
tebufenozide
teflubenzuron
triflumuron
1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenylurea, 1-(2,6-difluoro-benzoyl)-3-(2-fluoro-4-(1,1,2,2-tetrafluoroethoxy)-phenylurea and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-trifluoro-methyl)phenylurea.

11. Composition according to claim 1, characterized in that compound (B) is novaluron.

12. Composition according to claim 10, characterized in that the compound of IGR type is chosen from methoprenes, pyriproxyfens, lufenuron, hydroprene, cryromazine and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenylurea.

13. Composition according to claim 1, characterized in that the proportions, by weight, of compounds (A) of formula (I) and of compounds of type (B) are between 80/20 and 20/80.

14. Composition according to claim 1, characterized in that the fluid vehicle and the concentration of the compounds (A) and (B) are adapted to point application by deposition of "spot-on" type to the skin.

15. Composition according to claim 1, characterized in that the fluid vehicle and the concentration of the compounds (A) and (B) are adapted to local application by deposition of "pour-on" type to the skin.

16. Composition according to claim 1, characterized in that the fluid vehicle and the concentration of the compounds (A) and (B) are adapted to local application on a zone with a surface area of less than 10 cm^2, especially between 5 and 10 cm^2, in particular at two points and preferably localized between the animal's shoulders.

17. Composition according to claim 1, characterized in that it contains a dose of from 0.1 to 40 mg/kg of compound (A) and from 0.1 to 40 mg/kg of compound (B).

18. Composition according to claim 17, characterized in that it contains a dose of from 1 to 20 mg/kg, in particular from 2 to 10 mg/kg, of compound (A) and from 1 to 30 mg/kg, in particular 2 to 20 mg/kg, of compound (B).

19. Composition according to claim 14, characterized in that it also comprises a crystallization inhibitor (b), which is present in particular in a proportion of from 1 to 20% (W/V), preferably from 5 to 15%.

20. Composition according to claim 19, characterized in that the crystallization inhibitor (b) is chosen from:

- polyvinylpyrrolidone, polyvinyl alcohols, copolymers of vinyl acetate and vinylpyrrolidone, polyethylene glycols, benzyl alcohol, mannitol, glycerol, sorbitol, polyoxyethylenated sorbitan esters; lecithin,

sodium carboxymethylcellulose, acrylic derivatives such as methacrylates and the like,

- anionic surfactants such as alkaline stearates, in particular sodium, potassium or ammonium stearate; calcium stearate; triethanolamine stearate; sodium abietate; alkyl sulphates, in particular sodium lauryl sulphate and sodium cetyl sulphate; sodium dodecylbenzenesulphonate, sodium dioctylsulphosuccinate; fatty acids, in particular those derived from coconut oil,

- cationic surfactants such as water-soluble quaternary ammonium salts of formula $N^+R'R"R'"R"",Y^-$ in which the radicals R are optionally hydroxylated hydrocarbon radicals and Y^- is an anion of a strong acid such as the halide, sulphate and sulphonate anions; cetyltrimethylammonium bromide is among the cationic surfactants which can be used,

- amine salts of formula $N^+R'R"R'"$ in which the radicals R are optionally hydroxylated hydrocarbon radicals; octadecylamine hydrochloride is among the cationic surfactants which can be used,

- nonionic surfactants such as optionally polyoxyethylenated sorbitan esters, in particular polysorbate 80, polyoxyethylenated alkyl ethers; polyethylene glycol stearate, polyoxyethylenated derivatives of castor oil, polyglycerol esters, polyoxyethylenated fatty alcohols, polyoxyethylenated fatty acids, copolymers of ethylene oxide and propylene oxide,

- amphoteric surfactants such as substituted lauryl compounds of betaine,

or preferably a mixture of at least two of these crystallization inhibitors.

21. Composition according to claim 19, characterized in that it comprises a crystallization inhibitor couple formed by the combination of a film-forming agent of polymeric type and a surfactant, in particular in similar or identical amounts within the

limit of the total amounts of crystallization inhibitor.

22. Composition according to claim 21, characterized in that the film-forming agent is chosen from:

- the various grades of polyvinylpyrrolidone,
- polyvinyl alcohols, and
- copolymers of vinyl acetate and vinyl pyrrolidone,

and in that the surfactant is chosen from non-ionic surfactants, preferably polyoxyethylenated sorbitan esters, in particular the various grades of polysorbate.

23. Composition according to claim 14, characterized in that it comprises an organic solvent (c) having a dielectric constant of between 10 and 35, preferably 20 and 30, whose content in the overall composition preferably represents the difference to 100% of the composition.

24. Composition according to claim 23, characterized in that the organic solvent (c) is chosen from acetone, acetonitrile, benzyl alcohol, butyldiglycol, dimethylacetamide, dimethylformamide, dipropylene glycol n-butyl ether, ethanol, isopropanol, methanol, ethylene glycol monoethyl ether, ethylene glycol monomethyl ether, monomethylacetamide, dipropylene glycol monomethyl ether, liquid polyoxyethylene glycols, propylene glycol, 2-pyrrolidone, in particular N-methylpyrrolidone, diethylene glycol monoethyl ether, ethylene glycol, diethyl phthalate, or a mixture of at least two of these solvents.

25. Composition according to claim 23, characterized in that it also comprises an organic co-solvent (d) having a boiling point below 100°C, preferably below 80°C, and having a dielectric constant of between 10 and 40, preferably between 20 and 30, which is miscible with water and/or with the solvent (c), this co-solvent being present in particular in a

co-solvent (d)/solvent (c) weight/weight (W/W) ratio of between 1/15 and 1/2.

26. Composition according to claim 25, characterized in that the co-solvent (d) is chosen from absolute ethanol, isopropanol and methanol.

27. Composition according to claim 1, characterized in that it is made in the form of a kit combining, separately, in the same packaging, at least one container containing a compound (A) and at least one container for compound (B), and a notice specifying that the containers are to be used alternately with an interval, in particular of one month.

28. Composition according to claim 1, characterized in that it affords protection for 2 to 3 months.

29. Composition according to claim 2, in which the compound of formula (I) is such that R_1 is CN, R_3 is haloalkyl, R_4 is NH_2, R_{11} and R_{12} are, independently of each other, a halogen atom, and/or R_{13} is haloalkyl.

30. Composition according to claim 29, wherein X is $C\text{-}R_{12}$.

31. Composition according to claim 2, in which the compound of formula (I) is:
1-[2,6-Cl_2 4-CF_3 phenyl] 3-CN 4-[SO-CF_3]5-NH_2 pyrazole.

32. Composition according to claim 2, characterized in that the compound (B) is a compound which mimics juvenile hormones, in particular:

azadirachtin
diofenolan
fenoxycarb
hydroprene
kinoprene
methoprene
pyriproxyfen
tetrahydroazadirachtin
and 4-chloro-2-(2-chloro-2-methyl-propyl)-5-(6-iodo-3-pyridylmethoxy)pyridizine-3(2H)-one

or a chitin-synthesis inhibitor, in particular:

chlorfluazuron
cyromazine

diflubenzuron
fluazuron
flucycloxuron
flufenoxuron
hexaflumuron
lufenuron
tebufenozide
teflubenzuron
triflumuron
1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenylurea, 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(1,1,2,2-tetrafluoroethoxy)-phenylurea and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-trifluoro-methyl)phenylurea.

33. Composition according to claim 32, characterized in that the compound of IGR type is chosen from methoprenes, pyriproxyfens, lufenuron, hydroprene, cryromazine and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenylurea.

34. Composition according to claim 2, characterized in that the proportions, by weight, of compounds (A) of formula (I) and of compounds of type (B) are between 80/20 and 20/80.

35. Composition according to claim 2, characterized in that the fluid vehicle and the concentration of the compounds (A) and (B) are adapted to point application by deposition of "spot-on" type to the skin.

36. Composition according to claim 2, characterized in that it contains a dose of from 0.1 to 40 mg/kg of compound (A) and from 0.1 to 40 mg/kg of compound (B).

37. Composition according to claim 36, characterized in that it contains a dose of from 1 to 20 mg/kg, in particular from 2 to 10 mg/kg, of compound (A) and from 1 to 30 mg/kg, in particular 2 to 20 mg/kg, of compound (B).

38. Process for controlling fleas on small mammals, and in particular cats and dogs, over a long period, characterized in that the animal is treated by local application to the skin of parasiticidally effective

doses and proportions of a composition according to claim 1.

39. Process according to claim 38, wherein the compound (B) is a compound which mimics juvenile hormones, in particular:

azadirachtin
diofenolan
fenoxycarb
hydroprene
kinoprene
methoprene
pyriproxyfen
tetrahydroazadirachtin
and 4-chloro-2-(2-chloro-2-methyl-propyl)-5-(6-iodo-3-pyridylmethoxy)pyridizine-3(2H)-one

or a chitin-synthesis inhibitor, in particular:

chlorfluazuron
cyromazine
diflubenzuron
fluazuron
flucycloxuron
flufenoxuron
hexaflumuron
lufenuron
tebufenozide
teflubenzuron
triflumuron
1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenylurea, 1-(2,6-difluoro-benzoyl)-3-(2-fluoro-4-(1,1,2,2-tetrafluoroethoxy)-phenylurea and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-trifluoro-methyl)phenylurea.

40. Process according to claim 39, wherein the compound of IGR type is chosen from methoprenes, pyriproxyfens, lufenuron, hydroprene, cryromazine and 1-(2,6-difluorobenzoyl)-3-(2-fluoro-4-(trifluoromethyl)phenylurea.

41. Process according to claim 38, wherein compound (B) is novaluron.

42. Process according to claim 38, wherein the proportions, by weight, of compounds (A) of formula (I) and of compounds of type (B) are between 80/20 and 20/80.

43. Process according to claim 38, characterized in that the animal is treated by local point application to the skin of "spot-on" type.

44. Process according to claim 38, wherein it contains a dose of from 0.1 to 40 mg/kg of compound (A) and from 0.1 to 40 mg/kg of compound (B).

45. Process according to claim 38, wherein it contains a dose of from 1 to 20 mg/kg, in particular from 2 to 10 mg/kg, of compound (A) and from 1 to 30 mg/kg, in particular 2 to 20 mg/kg, of compound (B).

46. Process according to claim 38, wherein the animal is treated by depositing on the skin, in parasitically effective doses and proportions, a composition according to claim 2.

47. Process according to claim 38, wherein the animal is treated by depositing on the skin, in parasitically effective doses and proportions, a composition according to claim 8.

48. Process according to claim 38, for controlling ectoparasites, in particular ticks.

Insecticidal combination to control mammal fleas, in particular fleas on cats and dogs.

ABSTRACT

Process and composition, in particular for controlling fleas on small mammals, characterized in that the composition includes, on the one hand, at least one insecticide of 1-N-arylpyrazole type, in particular fipronil, and, on the other hand, at least one compound of IGR (insect growth regulator) type, in doses and proportions which are parasiticidally effective on fleas, in a fluid vehicle which is acceptable for the animal and convenient for local application to the skin, preferably localized over a small surface area.

Fig. None.

DECLARATION FOR USA PATENT APPLICATION

(including Design and National Stage PCT) Attorney's Docket ID: _____

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below adjacent to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled "Insecticidal combination to control mammal fleas, in particular fleas on cats and dogs".

_____, the specification of which

__X__ is attached hereto. (or)

_____ was filed on _____, [ ] and was amended on _____.

[ ] as U S Application No. _____ (or)

[ ] as International PCT Application No. _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 (a) - (d) or §365 (b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT International application which designated at least one country other than the United States of America, listed below and have also identified below, where priority is not claimed, any foreign application for patent or inventor's certificate, or any PCT International application, having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s) (_____ ADDITIONAL APPLICATIONS IDENTIFIED ON ATTACHED SHEET):

Number	Country	Day/Month/Year Filed	Priority ~~Not~~ Claimed
96 04 208	FRANCE	29 March 1996	Yes

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or §365(c) of any PCT International application designating the U.S., listed below; and insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application. (____ ADDITIONAL APPLICATIONS IDENTIFIED ON ATTACHED SHEET.)

Application Serial No.	Day/Month/Year Filed	Status -- patented, pending, abandoned

I hereby appoint the practitioners of **LARSON AND TAYLOR** associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number.

CUSTOMER NUMBER: 00881

Direct all telephone calls to _____, at TEL (703) 920-7200 (Fax: 703-892-8428)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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SIGN AND DATE HERE: Inventor's Signature:	Date:

Full Name of Third Joint Inventor, if any	Citizenship
Full Post Office Address	
Residence - City, State/Country (if different from P.O. address)	
SIGN AND DATE HERE: Inventor's Signature:	Date:

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Full Post Office Address	
Residence - City, State/Country (if different from P.O. address)	
SIGN AND DATE HERE: Inventor's Signature:	Date:

____ SEE ATTACHED SHEET FOR SIMILAR INFORMATION AND SIGNATURE FOR ADDITIONAL JOINT INVENTORS.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE Patent

In re application of **JEANNIN, P.**)
New Application) Atty's Dckt:
Filed: On even date herewith) Application Branch
For: INSECTICIDAL COMBINATION TO CONTROL MAMMAL FLEAS,...

PRELIMINARY AMENDMENT

Hon. Assistant Commissioner of Patents
Washington, D.C. 20231

S I R:

Preliminary to the examination thereof, please amend the above-identified application as follows:

IN THE CLAIMS:

46. (amended) Process [according to claim 38, wherein the animal is treated by depositing on the skin, in parasitically effective doses and proportions,] for controlling fleas on small mammals, and in particular cats and dogs, over a long period, characterized in that the animal is treated by local application to the skin of parasiticidally effective doses and proportions of a composition according to claim 2.

47. (amended) Process [according to claim 38, wherein the animal is treated by depositing on the skin, in parasitically effective doses and proportions,] for controlling fleas on small mammals, and in particular cats and dogs, over a long period, characterized in that the animal is treated by local application to the skin of parasiticidally effective doses and proportions of a composition according to claim 8.

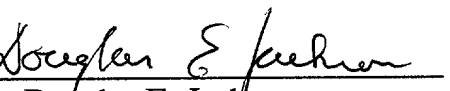
REMARKS

The above amendments to the claims are being made in order to reduce the filing fees and to place the application in better condition for examination.

Favorable consideration is respectfully requested.

Respectfully submitted,

Date: May 27, 1997



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